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14. ABSTRACT
Obesity has reached epidemic levels and yet the incidence continues to rise. The current study is seeking to examine the hypothesis that obesity may reflect dysfunctioning of the hypothalamic-pituitary-adrenal (HPA) axis in response to stressors. African American persons are at greatest risk, but reasons for this difference are unknown. We will study 120 men and women of Caucasian and African American ethnicity and examine their responses to physiologic stressors: exercise and ingestion of a meal. Methods: The HPA axis will be studied in some detail by using two stressor paradigms and two steroid regimens. We expect to be able to detect subtle differences in HPA axis reactivity in obese individuals that might contribute to morbidity and perhaps even make individuals resistant to therapeutic interventions. Results: We have enrolled 96 participants, with 66 completed. Data collection and analyses are proceeding on schedule. Two abstracts were submitted and accepted for presentation in Spring 2006. Conclusions: We are on schedule for all study milestones and look forward to being able to answer the important questions regarding the potential role of the HPA axis in obesity.

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obesity, insulin sensitivity, glucocorticoids, metabolic syndrome, African Americans, Caucasians, exercise, meal feeding

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INTRODUCTION

Obesity has reached epidemic levels and yet the incidence continues to rise. The current study is seeking to examine the hypothesis that obesity may reflect a dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis in response to stressors. African American persons are at greatest risk, but reasons for this difference are unknown. We will study 120 men and women of Caucasian (CA) and African American (AA) ethnicity to examine their responses to physiologic stressors: exercise and ingestion of a meal.

BODY

Year Three:

1. *Recruit, screen, and test 10 Non-obese subjects.*

Table 1. Breakdown of Normal Weight Participants by Ethnicity

Non-Obese	CA	AA
Screened	10	28
Recruited/Enrolled	3	9
In Progress	0	0
Dropped	1	4
Completed	**2**	**5**
Total Enrolled	**N = 12**	
Total Completed	**N = 7**	

2. *Recruit, screen, and test 30 Overweight/Obese subjects.*

Table 2. Breakdown of Overweight/Obese Participants by Ethnicity

Overweight (OW) & Obese (OB)	CA-OW	AA-OW	CA-OB	AA-OB
Screened	2	29	2	16
Recruited/Enrolled	1	12	3	7
In Progress	0	1	0	1
Dropped	0	5	1	2
Completed	**1**	**6**	**2**	**4**
Total Enrolled OW & OB	**N = 23**			
Total Completed OW & OB	**N = 13**			

We believe with our efforts from the previous years that we are on schedule as planned.

3. *Continue evaluating, reducing, and analyzing data.*

Multiple meetings have occurred among the PI, Co-investigators, with the Project Coordinator and other key staff on a regular basis to discuss issues and examine data collected on all completed subjects. Preliminary hormone, psychological, and other physiological data have been analyzed while preparing for two different abstracts to be presented at conferences this year. We are ahead of schedule for this goal.

4. *Begin biochemical analyses.*

Radioimmunoassay (RIA) analyses have continued on several of the different hormones of interest. Specifically, we have competed ACTH data on 13 subjects, Insulin data on 35 subjects, Cortisol (CORT) data on 21 subjects, and DHEA data on 26 subjects. Unfortunately, our manufacturer for the CORT kits stopped production and we had to find a new manufacturer. This caused us to start from the beginning and had to repeat testing on 15 subjects. We recently found the same manufacturing problem when we tried to order ACTH kits. Currently, we are still in the process of looking for a manufacturer and ACTH assays are temporarily on hold until we resolve this problem. We plan to continue the biochemical analyses on Insulin, CORT, and DHEA hormones and are on track for this goal.

5. *Begin statistical analyses on ethnicity.*

*D*ata have been gathered for the 66 subjects who have completed the study. From preliminary data analyses, weight, body mass index (BMI), and fasting blood glucose concentrations were not significantly different between AA and CA. However, despite similar weights and BMI, maximal aerobic capacity (VO_{2max}) was significantly lower in AA than CA (Table 3).

Table 3. Characteristics and Physiological Measures by Ethnicity

	AA (n=32)	**CA (n=34)**
Age (yrs)	29.4 ± 7.2	27.3 ± 5.2
Weight (kg)	84.6 ± 18.2	82.7 ± 20.3
BMI (kg/m^2)	28.3 ± 4.2	26.7 ± 5.0
VO_{2max} (kg/ml/min)	37.7 ± 9.6	44.8 ± 9.0 *
Glucose (mmol/L)	5.6 ± 1.0	5.4 ± 0.6

Values are mean ± SD.

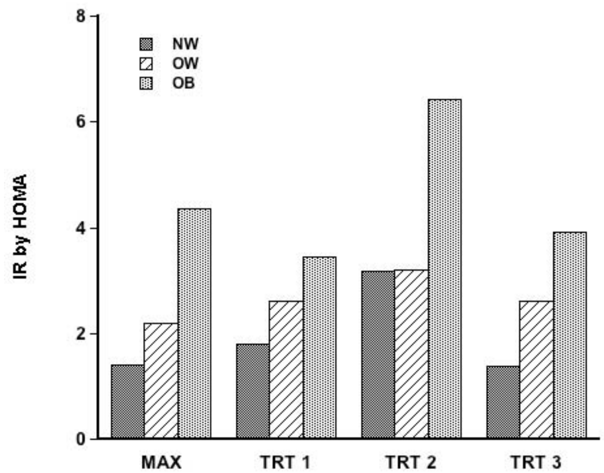
6. *Examine data on HPA reactivity from the exercise and meal challenge tests as a function of ethnicity after 15 AA and 15 CA subjects have been tested.*

We have CORT data on 25 subjects (9 AA and 16 CA). Because of the manufacturing problem with the production of CORT assay kits, we are still in the process of repeating and moving forward with the completion of the analyses on CORT. We have not yet examined the CORT data by ethnicity or BMI due to the small sample size. We expect to be caught up with this in the near future.

Despite new problems with the ACTH assay, we have preliminary data on 9 AA and 16 CA for visit 1 (meal challenge followed by maximal exercise test). It appears that CA have higher ACTH levels than AA, with CA men having the highest levels after exercise. ACTH did not increase in response to our meal. We plan to further explore the data once we get a larger sample size.

7. *Examine data describing HPA axis resistance to feedback control and insulin resistance as a function of ethnicity after 15 AA and 15 CA subjects have been tested.*

Figure 1. Insulin Resistance by HOMA Across Treatments by Weight Group



Insulin resistance (IR) was calculated by the homeostasis model assessment (HOMA) method, which is obtained by multiplying fasting insulin (μIU/mL) and glucose (mmol/L) levels and dividing the product by a constant (22.5). IR by HOMA was calculated for 12 AA and 23 CA (Figure 1). Preliminary analyses show that individuals with a higher BMI have a greater IR, which is consistent with the literature. Due to our small sample size, we have not yet analyzed the data by ethnicity.

8. *Examine data describing relation between exercise-associated increases in insulin sensitivity and glucocorticoid sensitivity as a function of ethnicity after 15 AA and 15 CA subjects have been tested.*

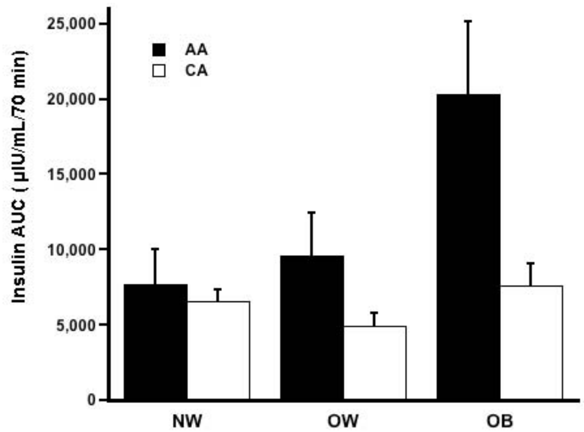
Areas under the curve (AUC) for insulin were calculated over the course of the meal challenge for all treatments. Preliminary analyses of the data showed significant differences between AA and CA across all three treatment groups. AA produced more insulin than CA for every treatment condition (Table 4). Individuals were grouped by BMI (normal weight (NW: 18≤25), over weight (OW: 25≤30), and obese (OB: 30≤38). Significant differences across BMI groups were also noted, with the OB releasing significantly greater amounts of insulin than NW and OW groups across all treatments (Table 4).

Table 4. Insulin AUC (μIU/mL/70min) by ethnicity and BMI (mean ± SE)

	TRT 1	**TRT 2**	**TRT 3**
AA *	9767 ± 1734	12456 ± 2429	8168 ± 1532
CA	4432 ± 599	6216 ± 549	3940 ± 461
NW	5276 ± 908	6805 ± 700	4500 ± 446
OW	5287 ± 1254	6794 ± 1348	4514 ± 1141
OB *	9916 ± 2271	13217 ± 3091	8466 ± 1929

Of great interest are the preliminary findings with treatment 2. Obese and overweight AA had the highest insulin production compared to all other groups for TRT 2 (Figure 2). In the future, we plan to calculate AUC for glucose and examine the ratio of the AUCs for insulin and glucose. Please note that we are not attempting to interpret these data, as the codes for treatment groups have not been officially broken.

Figure 2. Areas under Curve for Insulin by Body Mass Index Categories for Treatment 2



n = 3, 6, 4 AA; 13, 9, 5 CA; for NW, OW, OB, respectively

KEY RESEARCH ACCOMPLISHMENTS

- Screened 87 interested persons
- Presented abstract for American Psychological Association meeting in Washington, D.C. in August 2005
- Presented abstract for The Endocrine Society meeting in San Diego, CA in June 2005
- Prepared abstract for Society of Behavioral Medicine meeting in San Francisco, CA in March 2006.
- Enrolled 45 participants
- Completed testing 20 participants
- Completed biochemical analysis for ACTH on 13 subjects
- Completed biochemical analysis for Insulin on 35 subjects
- Completed biochemical analysis for Cortisol on 21 subjects
- Completed biochemical analysis for DHEA on 26 subjects
- Provided body composition services and recruited at the Healthy You Health and Fitness Expo in Silver Spring, MD in September 2005
- Prepared abstract for DoD conference in San Juan, Puerto Rico, May 2006

REPORTABLE OUTCOMES

We presented an abstract for the August 2005 American Psychological Association annual meeting that examined the associations among chronic stress, BMI, and ethnicity in 50 of our participants. There were 19 African-American (AA) and 31 Caucasian-American (CA) participants who completed a Stress Profile, which has subscales for chronic stress, healthy and lifestyle behaviors, and coping. Results of these 50 participants showed that chronic stress was positively related ($r = 0.67$, $p < 0.05$) to BMI among AA, but not CA ($r = -0.05$, ns), and this relationship was strongest among AA women ($r = 0.72$, $p < 0.05$). There was no relationship between BMI and Stress Profile subscales among CA, but BMI was significantly related to negative appraisal ($r = 0.50$, $p < 0.05$), cognitive hardiness ($r = -0.59$, $p < 0.05$), and psychological well being ($r = -0.48$, $p < 0.05$) among AA. The data we are collecting on the HPA axis will be critical for relating psychological data to a physiological context and developing a biological explanation.

A poster was presented at the June 2005 Endocrine Society annual meeting. Initial data on glucose and insulin responses by BMI group were included. Comparison among NW (n=16), OW (n=18), and OB (n=11) subjects revealed that peak glucose responses to exercise decreased with increasing BMI: OB subjects exhibited no significant increase in serum glucose during

exercise. The glucose response to the meal challenge in these subjects was comparable among the three groups. Both overweight and obese subjects showed relative insulin resistance, with the greatest effect for obese individuals under the Treatment 2.

An abstract was submitted and accepted for the March 2006 Society of Behavioral Medicine annual meeting. The abstract investigates physiological and psychological correlates of IR in 14 AA and 27 CA men and women. Physiological and psychological correlates of IR differed for AA and CA. In AA, IR was positively correlated with stress ($r = 0.54$) and negative appraisal ($r = 0.54$). In CA, IR was positively correlated with BMI ($r = 0.70$), WC ($r = 0.68$), body fat ($r=0.49$), and social support ($r=0.40$), and negatively correlated with exercise ($r = -0.40$) and VO_2max ($r = -0.62$). In AA, increasing levels of stress and negative appraisal were associated with greater IR. However, in CA, anthropometric measures and cardiovascular fitness were related to IR, and surprisingly, increasing social support was associated with greater IR. These findings may have implications for ethnic specific treatments for IR and obesity.

An abstract was prepared for the May 2006 Military Health Research Forum. The abstract discussed the physiological and behavioral correlates of obesity and insulin resistance (IR) as a function of ethnicity. Correlations for 32 AA and 34 CA were calculated for responses to the Stress Profile and the physiological variables of IR and waist hip ratio (W: H). IR was negatively associated with reported exercise habits ($r = -0.58$, $p = 0.03$,) and prevention strategies ($r = -0.78$, $p = 0.001$), and W:H was negatively associated with exercise habits ($r = -0.43$, $p = 0.04$) and health habits ($r = -0.48$, $p = 0.02$) for AA, but not CA. Correlations between IR and VO_{2max} and BMI were calculated in 14 AA and 27 CA. $VO_{2\ max}$ was significantly lower in AA than CA, despite similar weights and BMI. IR was inversely related to $VO_{2\ max}$ in both CA($r = -0.73$, $p < 0.05$) and AA($r = -0.54$, $p < 0.01$). IR was not related to BMI in AA ($r = 0.47$), whereas a strong and significant association was found in CA ($r = 0.82$, $p <0.05$). The behavioral correlates of obesity may provide important insights into the origins and causes of obesity among AA.

CONCLUSIONS

African Americans (AA) have the highest coronary heart disease mortality of any ethnic group in the United States, and AA women have a higher prevalence of Metabolic Syndrome than CA women. Our preliminary data indicate that obese men and women have several characteristics consistent with poor cardiovascular health, including lower maximal aerobic capacities and higher resting blood pressure, heart rates, and fasting glucose levels. Recently, our preliminary data indicate that AA are significantly less fit with respect to cardiovascular fitness levels than CA, despite similar weight and BMI.

In the two abstracts we are presenting in the upcoming months, intriguing results were seen for correlates of IR among AA. Overall, we find that anthropometric measurements and cardiovascular fitness measurements are related to IR. However, when we analyzed the data by ethnicity, these factors do not hold true for AA. IR was not related to BMI in AA, and the relationship between IR and VO_{2max} was not strong among AA. In addition, IR was negatively correlated with the psychological variables of exercise habits, prevention strategies in AA and positively correlated with stress and negative appraisal, but this was not true for CA. Also, W: H ratio was negatively associated with exercise habits and health habits in AA. These findings may have implications for ethnic-specific treatment for IR and obesity.

We previously reported in our Endocrine Society 2005 abstract that IR appears to be greater in obese individuals as compared to overweight participants under the 2nd treatment. We also

find that OB individuals produce a greater amount of insulin in response to the meal challenge measured as AUC. AA produced greater amounts of insulin across all treatment compared to CA. We found that in response to treatment 2, OB AA have the greatest insulin production compared to all groups. There was an effect of ethnicity and body type which may imply that there are less favorable health outcomes for those individuals who are both OB and AA.

Our goals for year three of this study included testing more participants, analyzing data, continuing biochemical and statistical analyses, and examining data for HPA reactivity, resistance to feedback control and insulin resistance, and exercise-associated increases in insulin and glucocorticoid sensitivity. We have successfully met these goals and are ahead of schedule in many areas. We have enrolled over 96 to date and have completed testing of 66 participants. We also submitted five abstracts and gave three poster presentations based on our physiological, biochemical, and psychological testing. Over the next two years we will continue to examine differences between CA and AA in terms of potential underlying causes of the metabolic syndrome and how different physiologic stressors activate the HPA axis and metabolic processes intrinsic to obesity and associated CHD risk factors. We will also start to examine the data as a function of gender and begin to prepare the report on the results.

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APPENDICES

None